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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/103,745	06/24/1998	SUDHIR AGRAWAL	IDRA-740US1	3401

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EXAMINER	
WOLLENBERGER, LOUIS V	

ART UNIT	PAPER NUMBER
1635	

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12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/103,745	AGRAWAL, SUDHIR	
	Examiner	Art Unit	
	Louis Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/8/2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 9/8/2009 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 4/28/2009 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Also acknowledged are Applicant's amendments to the claims filed 9/8/2009. With entry of the amendment, claims 16-19 are pending and examined herein.

Double Patenting—withdrawn

Upon further consideration, the rejection of Claims 16-19 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,476,000 is withdrawn. The patented claims are not considered to embrace a species of oligonucleotide within the scope of what is currently claimed in the instant application, 09/103745.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robert et al. (US 2001/0010899 A1).

Citing from US Provisional Application 60/021,041, Robert et al. taught CpG-containing phosphorothioate antisense oligonucleotides for inhibiting human papilloma viral gene expression in an infected host cell in a human (pp. 1-58; Tables 1A and B). Means and modes of administration to an individual of any of the antisense oligos are disclosed (page 1-58). In certain embodiments the anti-HPV oligonucleotides comprise a single CpG at the 3' end of the molecule. See for example the oligos referred to therein as HPV6 and HPV36, Table 1A, page 17. Robert et al. further explicitly and implicitly disclosed the phosphorothioate antisense oligonucleotides may be capped at their 3' and/or 5' ends with a nuclease resistance-conferring bulky substituent (page 14, beginning at line 29; see also disclosure at pages 11-14). Examples of such substituents are said to include a 2'-O-methyl, as shown in Table 1B (page 14, lines 29-38). Table 1B discloses at least two examples of phosphorothioate antisense oligonucleotides comprising one or two 2'-O-methyl modified nucleotides at the 3' end, reasonably implying that phosphorothioate antisense oligos may be modified with one or two 2'-O-methyl groups at the final one or two nucleotides at the 3' end of the oligonucleotide, as suggested by the disclosure.

See Oligos HPV1 OX2 and OX1 at Table 1B, page 26. See also disclosure at pages 34 and 35, describing the activities of 3'-end 2'-O-methyl modified phosphorothioates, i.e., hybrids. Accordingly, in view of Robert et al. as a whole, one of skill would reasonably have recognized and appreciated that an antisense phosphorothioate oligonucleotide may contain a 3' cap, such as a 2'-O-methyl, to enhance its resistance to nuclease degradation without compromising its antisense activity. Were one of skill to cap the final one or two nucleotides at the 3' end of oligonucleotide HPV6 or HPV36 with a 2'-O-methyl in the same manner generally suggested for any of the HPV oligos and exemplified therein for certain specific oligonucleotides, one of skill would necessarily obtain a modified CpG-containing oligonucleotide within the scope of the instant claims. Using the oligo in an individual in the manner taught by Roberts et al. would also necessarily provide all effects inherent to that oligonucleotide, including those recited in the claims, since a compound and its properties are inseparable. Thus, the public was reasonably in possession of a method within the scope of that now claimed at the time of invention.

One of skill would further have had reason to cap the 3' end of any of the phosphorothioate HPV antisense oligonucleotides disclosed by Robert et al. with a 2'-O-methyl in the manner taught by Robert et al. in view of Zhang et al., who had taught that PS-oligonucleotides are metabolized in various tissues (i.e., in vivo) primarily by 3'-exonucleases, and that degradation of PS-oligonucleotides in vivo reduces their effectiveness for longer duration. Zhang et al. further showed that oligonucleotide phoshorothioates having four 2'-O-methyl modified nucleotides at the 3' and 5' ends are more resistant to nucleases than the PS-oligonucleotide in vitro.

Accordingly, the prior art had suggested a method of making and using a 2'-O-methyl modified, CpG-containing phosphorothioate oligonucleotide within the scope of what is now claimed.

It is noted the instant claims as now written read on instances in the prior art wherein the CpG dinucleotide(s) occur(s) only at the 5' and/or 3' ends of the antisense oligonucleotide. The prior art described mixed backbone phosphorothioate oligos (gapmers and mixmers) comprising, in addition to phosphorothioate linkages, capping groups (including 2'-sugar modifications) at the 5' and/or 3' ends. In these cases, one of skill following these recommended practices would likely have been led to make and use an oligo within the scope of the claim, as demonstrated, for example, by Robert et al., even though one of skill did not set out to deliberately modify the C and/or G in the CpG for the purpose discovered by applicant.

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Claims 16-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cumin et al. (1993) *Eur. J. Biochem.* 212:347-354 in view of Matulic-Adamic et al. (US Patent 5,998,203); and Zhang et al. (1995) *Biochemical Pharmacology* 50:545-556.

Cumin et al. disclosed a 16-nucleotide, CpG-containing, antisense phosphorothioate for inhibiting the expression of human prorenin, said to be a possible target for drugs designed to lower blood pressure. See oligo F, Table 1, page 359. One of skill would reasonably infer the antisense oligos disclosed therein could be used for research purposes in cells in vitro and in vivo in an animal. In oligo F the CpG dinucleotide occurs at the 5' end of the antisense.

Cumin et al. do not teach modifying the CpG and only the CpG with a 2'-O-methyl.

However, one of skill would have had reason to modify the cytosine and/or guanosine in the CpG of oligo F in view of the prior art, which, at the time of invention, had taught that deoxy- and ribonucleic acids designed for inhibition of gene expression are more stable in vivo when they are chemically modified at the 5' and/or 3' ends.

For example, Matulic-Adamic et al. had taught the addition of a 5' and/or 3' end cap structure to DNAzymes and ribozymes (nucleic acids that cleave complementary DNA and RNA targets) protects the nucleic acids from exonuclease degradation and generally improves their stability in nuclease-rich environments. In one embodiment, the 5' cap is a 2'-O-methyl modified nucleotide (cols. 1-7; col. 3, lines 4-30; see definition of "alkyl" at column 5).

Accordingly, the prior art had suggested the incorporation of 5' capping groups, including 2'-O-methyl nucleotides, in therapeutic nucleic acids, as a general means to improve stability in vivo. It would therefore have been prima facie obvious to apply the same types of modifications to any known nucleic acid therapeutic, including any known antisense phosphorothioate for the same purpose with the reasonable expectation similar improvements in stability would be obtained. For example, at the time of invention, Zhang et al. had shown that the stability of a phosphorothioate antisense oligonucleotide could indeed be further improved by incorporation of 2'-O-methyl modified nucleotides at both ends of the molecule. In view of Matulic-Adamic et al., one of skill might reasonably have known that 2'-O-methyl modification of either end would lead to improvement. See for example, results at working example 4, col. 24, describing the effect of 5'-end modifications.

Accordingly, the prior art had suggested a method of using a 2'-O-methyl modified, CpG-containing phosphorothioate antisense oligonucleotide in vivo in an animal within the scope of the instant claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis Wollenberger whose telephone number is (571)272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tracy Vivlemore can be reached on (571)272-2914. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Louis Wollenberger/
Primary Examiner, Art Unit 1635
December 16, 2009